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STAGE 4S NEUROBLASTOMA TUMORS SHOW A CHARACTERISTIC DNA METHYLATION PORTRAIT

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Stage 4S neuroblastoma (NB) is a special type of NB found in infants with metastases at diagnosis and is associated with an excellent outcome due to its remarkable capacity to undergo spontaneous regression. As genomics have not been able to explain this intriguing clinical presentation, we here aimed at profiling the DNA methylome of stage 4S NB to better understand this phenomenon. To this purpose, differential methylation analyses between International Neuroblastoma Staging System (INSS) stage 4S, stage 4 and stage 1/2 were performed, using methyl-CpG-binding domain (MBD) sequencing data of 14 stage 4S, 14 stage 4, and 13 stage 1/2 primary NB tumors (all MYCN non-amplified in order not to confound results). Stage 4S-specific hyper- and hypomethylated promoters were determined and further characterized for genomic localization and function by cytogenetic band enrichment, gene set enrichment, transcription factor target enrichment and differential RNA expression analyses. We show that specific chromosomal locations are enriched for stage 4S differentially methylated promoters and that stage 4S tumors show characteristic hypermethylation of specific subtelomeric promoters. Furthermore, genes involved in important oncogenic pathways, in neural crest development and differentiation, and in epigenetic processes are differentially methylated and expressed in stage 4S tumors. Based on these findings, we describe new biological mechanisms possibly contributing to the stage 4S-specific tumor biology and spontaneous regression. In conclusion, this study is the first to describe the highly characteristic stage 4S DNA methylome. These findings open new avenues to further unravel the NB pathology in general and stage 4S disease specifically.